37 C.F.R. §1.17(a)(3) and 1.136(a). A Notice of Appeal is filed separately and concurrently herewith.

REMARKS

I. Form PTO-326

The Office Action Summary at page 1 incorrectly recites the pending claims. Claim 22 was canceled by a Supplemental Amendment, mailed 29 October 1999. Therefore, the correct recitation of pending claims is 1-11, 15, 16, 18-21 and 23-25.

II. Election/Restriction Requirement

The Examiner alleges that unity of invention requires "a special technical feature and a common core". The Examiner further alleges that the common core (-s=o-) of the claimed compound of formula I is not novel. Accordingly, the Examiner has made the restriction requirement final.

In a telephone discussion of December 14, 1999 between the Examiner and the undersigned attorney, the Examiner stated that the Examiner is relying upon Annex B of the Administrative Instructions under the PCT, in particular, subparagraph (f) entitled "Markush Practice", to support the position that unity of invention is lacking.

Applicants respectfully submit that the Examiner's reliance on the "Markush Practice" section of Annex B is misplaced. As such, the Examiner has ignored two material facts. Firstly, in the Amendment mailed 28 October 1999, Applicants amended independent claims 1, 7, 18 and 19 to recite the active ingredient as an H^+,K^+-ATPase inhibitor. The recitation of the H^+,K^+-ATPase inhibitor of the general formula I having a -s=o- core, which forms the basis for the

restriction requirement, was deleted from the independent claims and embodied in dependent claims 20, 21 and 23. Secondly, according to subparagraph (c) of Annex B of the Administrative Instructions under the PCT, entitled "Independent and Dependent Claims", it is expressly stated that, "***[u]nity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims***".

Thus, the Examiner has ignored the amended recitation of independent claims 1, 7, 18 and 19 which do not recite the compound of the formula I. Furthermore, the Examiner has failed to apply the correct rule in determining unity of invention. Independent claims 1, 7, 18 and 19 define the active ingredient as an H^+,K^+-ATPase inhibitor and do not recite the compound of the formula I. Accordingly, the Examiner's rationale for making the restriction requirement final in view of the previous claim amendment and the guidance offered by Annex B is improper.

Additionally, the Examiner statement that "Applicants core -s=o- is not novel" is immaterial. Indeed, the active ingredient of the claimed invention is not new, and therefore, the -s=o- core of the compounds of figure I is likewise not new. However, the patentable subject matter of the claimed invention is a new and nonobvious ***administration regimen*** of a known medicament. It is Applicants' discovery that the claimed ***administration regimen*** surprisingly induces an extended blood plasma profile of the H^+,K^+-ATPase inhibitor which brings about a measurable and advantageous improvement in the treatment of gastrointestinal disorders. The extended blood plasma profile of the H^+,K^+-ATPase inhibitor is the special technical feature linking the inventions of Groups I-IV as well as defining the patentability of the inventions of Groups I-IV over the prior art.

In summary, therefore, the restriction requirement is improper and should be withdrawn for the following reasons:

- The instructions concerning unity of invention as set forth in paragraph (c) of Annex B of the PCT administrative instructions clearly provides that unity of invention is to be considered only in relation to the independent claims and not the dependent claims.
- By Amendment, mailed 28 October 1999, the independent claims 1, 7, 18 and 19 were amended to define the active ingredient as an H^+,K^+-ATPase inhibitor.
- The extended blood plasma profile of the H^+,K^+-ATPase inhibitor is the special technical feature defining the inventions of Groups I-IV as well as defining the inventions of Groups I-IV over the prior art.

In view of the foregoing remarks, withdrawal of the election/restriction requirement is requested.

III. The Claimed Invention

Applicants wish to take this opportunity to clarify an important aspect of the claimed invention. On page 3-4 of the Office Action, the Examiner states that "[a] person skilled in the art would have been motivated to use extended release tablets, or other formulation to obtain an extended blood plasma profile, since it is well known that effect of H^+,K^+-ATPase inhibitors diminishes after a few hours". However, in view of this statement, it appears that the Examiner has failed to appreciate that there is no correlation between the plasma concentration and pharmacological effect of an H^+,K^+-ATPase inhibitor.

As disclosed on page 2, lines 16-20, of the specification, it is known that the duration of acid inhibition of one proton pump inhibitor, e.g., omeprazole, is 3-4 days despite a plasma half-life of only 0.5-1 hour (Lind et al., Gut 1983; 24:270-276). Notwithstanding a short plasma half-

life, there is an effective plasma concentration providing the patient with relief for at least 3-4 days. At the time the claimed invention was made, the prolonged duration of acid inhibition would have dictated against the administration of an extended release formulation as suggested by the Examiner. Specifically, in view of a duration of relief lasting 3-4 days, an extend release formulation of an H^+,K^+-ATPase inhibitor was seemingly unnecessary.

Accordingly, Applicants' claimed invention represents a divergence from the typical use of H^+,K^+-ATPase inhibitors in the treatment of gastrointestinal disorders. Moreover, it was Applicants' discovery that the unprecedented administration inducing an extended blood plasma profile of the H^+,K^+-ATPase inhibitor had an unexpected improvement in the inhibition of gastric acid secretion.

IV. Claim Rejection - 35 U.S.C. §102

The novelty rejection of record has been maintained. Accordingly, claims 1-11, 15, 16, 18 and 19 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Nos. 5,753,265 to Bergstrand et al. (the "'265 patent") and U.S. Patent No. 5,817,338 to Bergstrand et al. (the "'338 patent"). In support of the rejection, the Examiner cites the '265 patent at column 5, lines 33-38. Specifically, with regard to the cited disclosure of the '265 patent, the Examiner states that "[m]ultiple layered tablets inherently would give an extended release of dosage". To support the Examiner's interpretation of the '265 patent, the Examiner draws reference to U.S. Patent No. 5,945,124 to Sachs et al. (the "'124 patent").

Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. Applicants submit that neither the '265 and '338 patents discloses each and every element of the claimed invention. Moreover, the Examiner's reliance on the '124

patent to Sachs et al. in support of the novelty rejection is improper. Firstly, the Examiner cannot rely on the '124 patent to supplement the disclosure of the cited '265 or '338 patents. Anticipation must be found in a ***single*** reference. Secondly, as discussed below, the layered tablets of the cited '265 and '338 patents are not analogous to the slow-release tablets of the '124 patent to Sachs et al.

The '124 patent describes a slow release pharmaceutical formulation in the form of a layered tablet together with an anti-microbially active ingredient for treating a disorder caused by Helicobacter (See, claim 1). The layered tablet comprises (1) a core containing pantoprazole, (2) an intermediate layer which controls the release of pantoprazole and (3) an enteric coating. The presence of the release-slowing intermediate layer is critical to the layered tablet of the '124 patent. Specifically, the intermediate layer is a ***water-insoluble film*** that retards the release of the pantoprazole and, at the same time, acts as a barrier for interactions between the acid labile core material and the enteric coating (col. 4, lines 30-43).

By drawing reference to the '124 patent, it is apparent that the Examiner is of the mistaken opinion that the cited '265 and '338 patents are also directed to a slow release pharmaceutical formulation in the form of a multiple layered tablet. There is a significant disparity between the cited '265 and '338 patents and the disclosure of the '124 patent which cannot be ignored. As previously mentioned, the '124 patent requires the presence of a ***water-insoluble***, release-slowing intermediate layer. In contrast, the optional separating layer between the core material and the enteric coating layer of the multiple unit tablets of the cited '265 and '338 patents is a ***water-soluble or insoluble but disintegrating in water*** layer (See claim 11 of the '265 patent; claim 22 of the '338 patent). Therefore, it is meaningless to rely on the '124 patent to interpret the cited '265 and '338 patents, or vice versa, as the Examiner has done.

The cited '265 and '338 patents are directed to a multiple unit tablet comprising enteric coating layered units wherein the enteric coating layer possesses advantageous physical properties that preserve the integrity of the units during compression and facilitate the transfer of the acid labile active ingredient in an intact form to the desired site of activity, i.e., the proximal part of the small intestine. Applicants submit that the '265 and the '338 patent are not directed to the special technical feature of the claimed invention, i.e., a repeated regimen or dosage form which provides an extended plasma blood profile of an H^+,K^+-ATPase inhibitor to maximize the effectiveness of the active ingredient. Applicants respectfully request the Examiner to reconsider the Remarks appearing on pages 23-26 of the Amendment, mailed 28 October 1999.

Specifically, claims 1-6 and 18 are directed to an administration regimen which induces an extended blood plasma profile of an H^+,K^+-ATPase inhibitor. Although the '265 and '338 patents suggest that a daily dose can be administered one to several times a day (See the '265 patent at col. 10, lines 36-42; the '338 patent at col. 8, lines 59-61), neither of the references is directed to the special technical feature of the claimed invention, i.e., a repeated regimen or dosage form which provides an extended blood plasma profile of an H^+,K^+-ATPase inhibitor to maximize the effectiveness of the drug. The administration regimen of the '265 and '338 patents is consistent with the typical administration regimen of pharmaceuticals, i.e., increase the dosage or frequency to increase the pharmacological effect of the drug. Typically, a single dose of omeprazole is prescribed and administered due to the long duration of gastric acid inhibition. In instances where a single daily dose is inadequate to provide relief, the doctor may prescribe repeated single dosages every 12 hours.

However, the pharmacological effect of a proton pump inhibitor, such as omeprazole, is not dependent on the plasma concentration of the drug itself. For example, whereas the duration

of acid inhibition of omeprazole is 3-4 days, the plasma half-life of the same drug is only 0.5-1 hour. Therefore, it is indeed contrary to the '265 and '338 patents that the pharmacological effect of a proton pump inhibitor could be significantly improved, as demonstrated by the Example and Figure of the subject application, by a repeat regimen of an H^+,K^+-ATPase inhibitor. As disclosed in the specification at page 5, lines 6-15, the administration regimen of the claimed invention also encompasses an extended and constant release of the H^+,K^+-ATPase inhibitor which follows the pharmocokinetics of the repeat administration of the Example. Neither the '265 nor the '338 patent discloses these aspects of the claimed invention as particularly embodied by claims 1 and 2.

Additionally, claim 3 recites a specific administration regimen having ***a dosage interval of 0.5-4 hours***. The recited feature of claim 3 or the effect of such an administration regimen is not disclosed, in the '265 or '338 patents. Therefore, there is no anticipation.

The administration regimen of claim 4 is based on the ***absorption of the proton pump inhibitor in two or more discrete pulses separated in time by 0.5-4 hours***. The recited feature of claim 4 is not disclosed in the '265 or '338 patents. Therefore, there is no anticipation.

As recited by claim 5, the proton pump inhibitor is released for a***bsorption with an almost constant rate during an extended time period and the extended plasma profile is maintained for 2-12 hours***. The recited feature of claim 5 is not disclosed in the '265 or '338 patents. Therefore, there is no anticipation.

Claim 6 recites ***an extended plasma profile of 2-12 hours***. The recited feature of claim 6 is not disclosed in the '265 or '338 patents. Therefore, there is no anticipation.

Claims 7-11 and 19 are directed to an oral pharmaceutical formulation which induces an extended blood plasma profile of an H^+, K^+-ATPase inhibitor. As previously discussed, the '265 and '338 patents disclose that the single dosage form may be administered one to several times a

day. However, there is no disclosure of a pharmaceutical formulation wherein the drug is administered to give ***an extended release*** blood plasma profile.

The PCT family member (WO 96/01623) of the cited '338 patent was cited against the formulation claims of the international application from which the subject national stage application derives. The Examiner's attention is directed to the International Preliminary Examination Report where it is stated that the formulation claims are both novel and non-obviousness in view of WO 96/01623. The dosage forms of the '265 and '338 patents may be administered one to several times a day. However, the drug is not administered by a regimen to provide an extended blood plasma profile. Therefore, the cited references fail to disclose each and every element of the claimed pharmaceutical formulation as described by claims 7-11and 19. Therefore, there is no anticipation.

Claims 15 and 16 are directed to methods of treatment comprising the administration of the pharmaceutical formulation of claims 7-11. Applicants submit that claims 15 and 16 are novel for the same reasons that the composition claims 7-11 and 19 are novel in view of the cited '265 and '338 patents.

For all of the foregoing reasons, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 102(e).

V. Claim Rejection - 35 U.S.C. §103

The obviousness rejection of record has been maintained. Accordingly, claims 1-11, 15, 16, 18 and 19 are rejected under 35 U.S.C. §103(a) as being unpatentable over the '265 and '338 patents.

As discussed in the preceding Section IV, the Examiner is of the mistaken opinion that the cited '265 and '338 patents are directed to a multiple layered tablet giving an extended release of the active ingredient. Rather, ***the '265 and '338 patents are directed to a multiple unit tablet comprising an enteric coating layer having mechanical properties such that the acid resistance of the enteric coating layered unit is not significantly affected by compression during tableting*** (See claim 1 of '265 and '338 patents). Therefore, if the '265 and '338 patents are not directed to a delayed release formulation, then it is axiomatic that the '265 and '338 patents cannot provide any meaningful suggestion of the claimed administration regimen and pharmaceutical formulation for inducing an extended blood plasma profile of a proton pump inhibitor. Furthermore, in view of the prolonged degree and duration of acid inhibition of omeprazole, e.g., 3-4 days, it was indeed unexpected that a repeated regimen or a dosage form which provides an extended blood plasma concentration of an H^+,K^+-ATPase inhibitor, as claimed, would have an improved pharmacological effect in the inhibition of gastric acid secretion. This advantage and unexpected result is not suggested by the cited '265 and '338 patents.

Moreover, as noted by the Examiner in the international application from which the subject national stage application derives, the PCT family member (WO 96/01623) of the cited '338 patent discloses the general state of the prior art and, therefore, does not suggest the advantage which is possible with the claimed invention. The prolonged pharmacological effect of an H^+,K^+-ATPase inhibitor would not have suggested the need or advantage of a repeated regimen or dosage form which provides an extended blood plasma concentration of the proton pump inhibitor. Applicants rely on the Example and Figure which substantiate the unexpected advantage of the claimed invention. It is submitted that the cited '265 and '338 patents do not suggest the pharmacokinetic phenomena that is represented by the Figure.

For all of the foregoing reasons, withdrawal of the rejection under 35 U.S.C. §103(a) in view of the '265 and '338 patents is requested.

New Rejections

VI. Claim Rejections - 35 U.S.C. §102

Claims 1-11, 13 and 19-25 are rejected under 35 U.S.C. §102(e) as being anticipated by the '265 patent.

Applicants submit that this so-called "new rejection" is essentially the same as the novelty rejection of record which is also based on the '265 patent as discussed in Section IV. The only difference is the claims against which the so-called "new rejection" has been applied. Specifically, the rejection of claims 1-11 and 18 under 35 U.S.C. §102(e) as being anticipated by the '265 patent is not new. The rejection against claims 13 and 22 is moot as theses claims have been canceled. Therefore, the so-called "new rejection" is new only as applied to dependent claims 20, 21 and 23-25. The Examiner is requested to make the necessary corrections so that the record accurately reflects the disposition of the claims.

Claims 20, 21 and 23-25 were added by the Amendment, mailed 28 October 1999, and the Supplemental Amendment, mailed 29 October 1999. Applicant submits that the so-called "new rejection" is improper for the same reasons set forth in the preceding Section III in connection with independent claims 1, 7, 18 and 19 from which claims 21, 21 and 23-25 ultimately depend.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 102(e).

VII. Claim Rejections - 35 U.S.C. §103

Claims 1-11, 13 and 18-25 are rejected under 35 U.S.C. §103 as being unpatentable in view of the '265 patent in combination with the following secondary references: (a) the '124 patent to Sachs et al.; (b) Remington's Pharmaceutical Sciences, John Hoover, 1975, p. 702; (c) Scand. J. Gastroenterol., Lind et al. 1986, p.137-138; (d) Scand. J. Gastroenterol., Lind et al., 1988, 23, p.1259-1266; and (e) Lind et al., Gut, 1983, p. 270-276.

Applicants submit that the Examiner has not established a *prima facie* case of obviousness. Specifically, there is no motivation to combine the primary reference ('265 patent) and the secondary reference ('124 patent). The '124 patent requires the presence of a ***water-insoluble***, release-slowing intermediate layer. In contrast, the optional separating layer between the core material and the enteric coating layer of the multiple unit tablets of the cited '265 patent is expressly a ***water-soluble or insoluble but disintegrating in water*** layer (See claim 11 of the '265 patent). It is evident, therefore, that the intermediate layers of the '265 and '124 patents are different and have a different effect. Accordingly, the cited art is nonanalogous and the required motivation is lacking to use the concept of the '124 patent with the multiple unit tablets of the '265 patent.

Moreover, as previously discussed, the pharmacological effect of an H^+,K^+-ATPase inhibitor is not correlated to the plasma concentration of the same drug. Notwithstanding a short plasma half-life, i.e., 0.5-1 hour, there is an effective plasma concentration providing relief for at least 3-4 days. The prolonged duration of acid inhibition would have dictated against the administration of an extended release formulation as suggested by the Examiner.

The cited prior art publications, as discussed in the specification, represent the general state of the art at the time the invention was made. Lind et al. in Gut disclose that the duration of

acid inhibition of one proton pump inhibitor, e.g., omeprazole, is 3-4 days despite a plasma half-life of 05.-1 hour (See, specification at p.2, lines 16-18). In the cited articles from the Scand. J. Gastroenterol., Lind et al. disclose that a single daily dosage of omeprazole results in 75-80% inhibition of maximal acid output prior to the next dose. Therefore, about 20-25% of the maximal gastric acid secretory capacity is present 24 hours after a daily dose of the drug. Thus, even if an increased dosage of the proton pump is administered, the maximal gastric acid inhibition is limited to about 80% (See, specification at page 3, lines 26-31). The Remington article provides a general discussion of the relationship between "duration of action" and pharmokinetics of a drug.

For all of the foregoing reasons, the Examiner has not established a *prima facie* case of obviousness. There is no motivation to combine the '265 and '124 patents, and the cited publications do not overcome any deficiencies of the '265 and '124 patents, whether taken alone or in combination. Withdrawal of the rejection under 35 U.S.C. §103(a) in view of the '265 patent in combination with the '124 patent and the other secondary references is requested.

Applicants would welcome the opportunity of an interview with the Examiner to clarify, where necessary, aspects of the invention and/or prior art.

CONCLUSION

The Remarks set forth herein are fully responsive to the Office Action. It is respectfully submitted that claims 1-11, 15, 16, 18-21 and 23-25 are in condition for allowance, which action is earnestly solicited.

Any additional fee in connection with this response should be charged to Deposit Account No. 23-1703.

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